REMARKS

Applicants respectfully request entry of the above amendments to Claims 1, 10, 11, 26 and 27; cancellation of Claims 5-7 and 9; and the entry of new Claims 85-89. With entry of the requested amendments, Claims 1, 10, 11, 23-27 and 85-89 are pending.

Claim 1 has been amended to more clearly indicate the subject matter of the claim. The amendment to Claim 1 finds support, for example, in the specification at page 6, lines 13-14; page 13, lines 10-14; page 22, lines 3-11; Examples 2 and 3; Claim 9 as originally filed; and elsewhere in the specification and claims as filed.

Claim 26 has been amended for clarity and to be independent. The amendment to Claim 26 finds support in the specification, for example, at page 9. lines 9-14; page 22, lines 3-11; original Claim 9; and elsewhere in the specification and claims as filed.

Claim 27 has been amended to be an independent claim. The amendment to Claim 27 finds support in the specification, for example, at page 9. lines 3-8; page 22, lines 3-11; original Claim 9; and elsewhere in the specification and claims as filed.

New Claims 85-89 depend from independent Claim 27 and find support in the specification and claims as originally filed, for example, being supported in the specification at page 6, lines 11-29 page 7, lines 1-5 and 28-30; page 8, lines 1-9; page 13, lines 10-14 and lines 24-26; original Claim 9; and elsewhere in the specification and claims as filed.

No new matter is added by way of the amendments to the specification or claims.

Claims 26 and 27 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention; Claims 1-3, 5-11, and 23-27 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not reasonably providing enablement for methods of controlling excessive proliferation or migration of smooth muscle cells *in vitro* comprising treating said smooth muscle cells with an effective

amount of an antibody antagonist of a native ErbB4 receptor of SEQ ID NO.: 2; Claims 26 and 27 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite and ambiguous in the recitation of the phrase "antibody binds essentially the same epitope as an antibody produced by ..."; Claims 1-3, 5-11 and 23-27 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over US Patent No. 5,811,098 in view of Krymskaya (1999) or Godowski, WO 99/02681, for the reasons set forth in the previous Office Action.

Applicants respectfully traverse the rejections.

The Rejections of Claims 26 and 27 Under U.S.C. §112, First Paragraph - Regarding Hybridoma Deposit

Claims 26 and 27 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention. In making this rejections, the Examiner referred to the deposit of hybridoma lines discussed in the specification. Applicants note that antibodies suitable for the practice of the invention include, but are not limited to, the particular hybridoma lines discussed in the specification. Thus, Applicants respectfully disagree with the Examiner's suggestion that "an antibody produced by a hybridomas [sic] HER4.10H1.1A1, HER4.1C6A11, HER4.3B9.2C9, HER4.1A6.5B3, and HER4.8B1.2H2are required to practice the claimed invention" (page 3, lines 6-7). Although the antibodies produced by these hybridomas are among those antibodies suitable for the practice of the invention, they are not the only suitable antibodies.

The Examiner stated "the enablement requirements of 35 U.S.C. §112, first paragraph, may be satisfied by a deposit of the pertinent hybridomas which produce these antibodies" (point 8, first paragraph, lines 5-7).

Applicants draw the Examiner's attention to pages 78 to 79 of the specification as filed. Page 78, lines 2-23 discloses that the hybridomas HER4.10H1.1A1 (ATCC Accession Number PTA-2828), HER4.1C6.A11 (ATCC Accession Number PTA-2829), HER4.3B9.2C9 (ATCC Accession Number PTA-2826), HER4.1A6.5B3 (ATCC

Accession Number PTA-2827) and HER4.8B1.2H2 (ATCC Accession Number PTA-2825) have been deposited with the ATCC. The complete name and address of the depository (American Type Culture Collection, 10801 University Blvd., Manassas, Va. 20110-2209, USA (ATCC)) was disclosed in the specification (page 78, lines 4-5). The deposit was made on December 19, 2000, as disclosed in the specification at page 78, lines 5-11. The deposit was made under the provisions of the Budapest Treaty (page 78, lines 12-15) and will be maintained for 30 years (page 78, line 15). The deposit will be made available to the public by the ATCC under the terms of the Budapest Treaty (page 78, lines 15-23). A copy of the ATCC deposit receipt and a statement that the deposit has been made under the terms of the Budapest Treaty over the signature of an attorney of record is enclosed with this Amendment.

Accordingly, Applicants respectfully submit that the rejections of Claims 26 and 27 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to be enabling is overcome.

The Rejections of Claims 1-3, 5-11 and 23-27 Under U.S.C. §112, First Paragraph - Regarding Controlling Excessive Proliferation or Migration

Claims 1-3, 5-11, and 23-27 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not reasonably providing enablement for methods of controlling excessive proliferation or migration of smooth muscle cells *in vitro* comprising administering an effective amount of an antibody antagonist of a native ErbB4 receptor of SEQ ID NO.: 2.

Applicants acknowledge the Examiner's statement that the specification is "enabling for a method of partially inhibiting controlling proliferation or migration of smooth muscle cells *in vitro* comprising administering an effective amount of an antibody to native ErbB4 receptor of SEQ ID NO.: 2" (page 3, point 9, first paragraph, line 2-3). As amended, independent Claims 1, 26 and 27 recite "A method for inhibiting proliferation or migration of vascular smooth muscle cells comprising treating said vascular smooth muscle cells with an effective amount of an antibody antagonist of a native ErbB4 receptor of SEQ ID NO.: 2." The phrase "inhibiting an ErbB4 (HER4)

receptor" is discussed in the specification, for example, at page 22, lines 3-11, and includes a wide range of amounts of inhibition. Applicants submit that the subject matter of Claims 1, 26 and 27 is enabled by the specification (see, for example, page 6, lines 11-16; page 13, lines 10-14; page 68, lines 3-10 and Fig. 5; page 68, lines 26-29 and Fig. 6). Applicants further submit that the subject matter of dependent Claims 5-7, 9-11 and 23-27 is also enabled in the specification.

For example, the data presented in Examples 2 and 3 and Figures 5 and 6 of the specification demonstrate inhibition of proliferation of target cells by an antibody antagonist of a native ErbB4 receptor of SEQ ID NO.: 2 and thus supports the inventions of Claims 1, 26, 27 and their dependent claims which are directed to a method for inhibiting proliferation or migration of smooth muscle cells comprising treating said smooth muscle cells with an effective amount of an antibody antagonist of a native ErbB4 receptor of SEQ ID NO.: 2. One of ordinary skill in the art, following the teachings of the specification, including but not limited to the noted Examples, would thus be able to practice the claimed invention by duplicating the examples, or by modifying them in ways known to one of ordinary skill in the art (*e.g.,* by increasing the amount of antibody antagonist of a native ErbB4 receptor of SEQ ID NO.: 2). Applicants thus submit that the claimed invention is enabled to the full scope of the claims.

The Examiner, objecting to the term "controlling" in the claims, suggests that "total prevention of excessive proliferation and migration of smooth muscle cells ... was not achieved" (page 4, lines 22-23 of the Office Action). Applicants note that the present claims do not include the term "controlling." Applicants further note that the specification clearly provides examples of inhibition of proliferation or migration of smooth muscle cells as required by the present claims. Moreover, the present application includes data showing that increasing amounts of ErbB4 antagonist antibodies produce concomitantly increasing amounts of inhibition, demonstrating a dose-dependent effect of the ErbB4 antagonists. Thus, there is clear support in the specification for the inhibition of proliferation and migration of smooth muscle cells as recited in the claims.

In addition, Applicants respectfully submit that there is no requirement that applicants provide an example of "total prevention." For example, in a case where claims had been rejected under 35 U.S.C. §112, first paragraph (*In re Cortright*, 165 F.3d 1359, 49 USPQ2d 1464 (Fed. Cir. 1999)), the Federal Circuit found that an applicant did not need to demonstrate a "complete" cure of baldness, and that the claimed method was supported by the specification to the full breadth of the claims, where the claimed methods was directed to a method to "restore hair growth." Applicants submit that the present specification, which provides examples of inhibition of proliferation or migration of smooth muscle cells, supports and enables the breadth of the claims to a method for inhibiting proliferation or migration of smooth muscle cells.

Applicants note that the data presented in the application include *in vitro* data, and that one of ordinary skill in the art would know that such *in vitro* data indicates that similar effects would be expected from administration of the ErbB4 antagonists *in vivo.* The court in *in re Brana* 51 F.3d 1560, 1565 (Fed. Cir. 1995), discussing *in vitro* tests using tumor cells lines, disagreed with claim rejections based on an argument that cell lines were not "diseases", instead concluding that "these tumor models represent a specific disease against which the claimed compounds are alleged to be effective." Applicants respectfully submit that the disclosure of the present specification enables one of ordinary skill in the art to make and use the claimed invention, including to inhibit excessive proliferation and migration of smooth muscle cells. Such inhibition can occur both *in vitro*, as explicitly demonstrated in the specification, and *in vivo*, as would be recognized by one of ordinary skill in the art based on the present disclosure.

For example, in *in re Brana*, Id. at 1566, the court cited *in re Marzocchi* 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971) and stated "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support." Applicants respectfully submit that there is no reason to doubt the objective

truth of the statements in the specification, and note that the Examiner has not suggested that there might be any reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support.

Thus, the specification demonstrating inhibition of proliferation or migration of smooth muscle cells, which is subject matter sought to be patented, and there being no reason to doubt the objective truth of that demonstration, applicants respectfully submit that the rejection to Claims 1-3, 5-11 and 23-27 under 35 U.S.C. §112, first paragraph, as allegedly not reasonably providing enablement for the claimed methods is overcome.

The Rejections of Claims 26 and 27 Under 35 U.S.C. §112, Second Paragraph

Claims 26 and 27 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims have been objected to as allegedly indefinite and ambiguous in the recitation of "antibody binds essentially the same epitope as an antibody produced by ...," the Examiner alleging that "essentially the same epitope" is unclear, indefinite and not disclosed in the specification.

Applicants draw the Examiner's attention to the discussion relating to epitopes on pages 21 and 22 of the specification, including the phrase "essentially the same epitope" (discussed on page 22, lines 26-30 and page 23, lines 1-2). Where a first antibody binds to an identical, or to a sterically overlapping, epitope, as does a second antibody, the two antibodies are said to bind to essentially the same epitope. Methods for determining whether two antibodies bind to the identical, or to sterically overlapping, epitopes, are also discussed; such methods include competition assays, which may use, for example, radioactive or enzyme labels.

Thus, Applicants respectfully submit that the phrase that has been objected to is defined in the specification, as noted above. Applicants further submit that the phrase in not unclear. Due to the disclosure and description of the present specification and to the knowledge of one of ordinary skill in the art, Applicants respectfully submit that the meaning of the phrase "essentially the same epitope" would be understood by one of

ordinary skill in the art. Applicants note, for example, that the specification teaches how to determine whether two antibodies bind to essentially the same epitope.

In addition, Applicants note that claims in issued U.S. patents include the phrase "binds to substantially the same epitope" (US 6,703,020), "specifically binds to the same epitope" (6,657,050), "binds to the same epitope" (6,403,090; RE38,008), and similar phrases. Thus, such phrases being acceptable in claims allowed by the United States Patent and Trademark Office, Applicants submit that the phrase "binds to essentially the same epitope" is definite and not ambiguous.

Accordingly, Applicants respectfully submit that the rejection to Claims 26 and 27 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite and ambiguous is overcome.

The Rejections Under 35 U.S.C. §103(a)

Claims 1-3, 5-11 and 23-27 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over US Patent No. 5,811,098 in view of Krymskaya (1999) or Godowski, WO 99/02681, for the reasons set forth in the previous Office Action. Applicants respectfully traverse these rejections, and submit that the cited references when taken together fail to make the claimed invention obvious.

In order to establish a prima facie case of obviousness, there must be 1) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on the Applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

For the sake of brevity, Applicants' remarks and arguments presented in prior papers regarding the rejections of the claimed inventions as allegedly being obvious over US Patent No. 5,811,098 in view of Krymskaya or WO 99/02681 are hereby incorporated by reference.

The Examiner has stated that Applicants "argue the references individually and not their combination" and refers to *In re Young* to state that "[o]ne cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references." Applicants believe that previous arguments were directed both at the references individually *and* in combination; as discussed below, Applicants submit that even taken in combination, the cited references fail to make obvious the claimed invention.

Claim 1 recites "A method for inhibiting proliferation or migration of vascular smooth muscle cells comprising treating said vascular smooth muscle cells with an effective amount of an antibody antagonist of a native ErbB4 receptor of SEQ ID NO.: 2."

US Patent No. 5,811,098 lacks elements of the claimed invention. It is, in part, directed to the identification and characterization of HER4, the "fourth member of the EGFR family (column 4, line 29). Although Plowman et al. note in US Patent No. 5,811,098 that "Northern and in situ hybridization analyses localizes HER4 to the white matter and glial cells of the central and peripheral nervous system, as well as to cardiac, skeletal, and smooth muscle." (column 42, lines 59-62), there is no further discussion of smooth muscle cells, and there is no mention of vascular smooth muscle cells in the reference at all.

The Examiner notes that US Patent No. 5,811,098 does not teach a method of controlling excessive proliferation or migration of smooth muscle cells *in vitro.* In addition, although it discusses antibodies to HER4, the '098 patent nowhere discusses inhibiting proliferation or migration of smooth muscle cells; and in particular, the '098 patent nowhere discusses inhibiting proliferation or migration of *vascular* smooth muscle cells.

Thus, the '098 patent lacks at least the element of inhibiting proliferation or migration of vascular smooth muscle cells. The other references, including all three references combined together, do not make up for the absence of this claim element.

Krymskaya cannot be taken as disclosing the claimed methods since it explicitly teaches that ErbB4 receptors are inactive, and that ErbB4 ligands (*e.g.,* EGF) do NOT

affect them. In fact, Krymskaya teaches *away* from the claimed invention, teaching that the ErbB4 receptor on human airway smooth muscle cells does NOT affect proliferation (Krymskaya, page L252, column 2, lines 7-9: "... in quiescent HASM [human airway smooth muscle] cells, ErbB-3 and ErbB-4 are functionally inactive" and at page L248, column 2, lines 37-39: "ErbB-3 and ErbB-4 in EGF-stimulated cells did not appear to be activated"). In addition, Krymskaya does not discuss vascular smooth muscle.

Thus Krymskaya fails to make up for the missing teachings of the '098 patent, so that the combination of the '098 patent with Krymskaya fails to provide all the elements of the claimed invention.

WO 99/02681 cannot be taken as disclosing the claimed methods, since, although the presence of ErbB4 receptors are noted on smooth muscle cells (page 8, lines 38-39), vascular smooth muscle cells are not noted. It is noted that a "neutralizing antibody" may block possible mitogenic activity of NRG3 to activate an ErbB4 receptor in a cell proliferation assay (page 17, lines 27-31); however, the "neutralizing antibody" referred to in WO 99/02681 is directed against the ligand NRG3, and not against an ErbB4 receptor as in the present invention. Thus, for at least the reason that it nowhere suggests that antagonists to ErbB4 receptors might be useful to inhibit vascular smooth muscle proliferation, WO 99/02681 also fails to provide missing elements. Thus WO 99/02681 fails to make up for the teachings missing from both the '098 patent and from Krymskaya.

The combination of all three cited references lacks disclosure or suggestion of treatment using an antibody antagonist of a native ErbB4 receptor of SEQ ID NO.: 2 directed at a smooth muscle cell for inhibiting proliferation or migration of that cell. As discussed previously, none of the references disclose such treatment of smooth muscle cells; and taken together, the combination of the cited references also fails to provide the claimed invention.

Thus, the combination of these references, none of which is directed to vascular smooth muscle cells, one of which is directed to the identification and characterization of HER4, one of which teaches away from the claimed invention by teaching that ErbB4 receptors are inactive in smooth muscle cells, and one of which discusses antibodies to

ErbB4 ligands but not ErbB4 receptors, in no way provides the present invention. The combination of all three cited references fails to provide all the elements of the claimed invention, lacking at least the missing teachings of inhibiting proliferation or migration of smooth muscle cells.

In addition, as discussed previously, the cited references provide no motivation nor suggestion to be combined, being directed to different arts and having different aims, one being directed to the identification and characterization of HER4, one being directed to ligands of the ErbB4 receptor and not the receptor itself, and the third teaching that the ErbB4 receptors of smooth muscle are inactive so that interaction with them would be futile in treatments directed at inhibiting proliferation of smooth muscle.

Lacking the elements of the claimed invention, and lacking any suggestion to be combined to provide the claimed invention were they to have provided such elements, a combination of the cited references fails to make the claimed invention obvious.

As was also discussed previously, for at least the reasons discussed above, one of ordinary skill in the art would have no reasonable expectation of success even if the references were to be combined.

"Combining prior art references without evidence of such a suggestion, teaching or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight." In re Dembiczak, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999). Applicants respectfully submit that none of the cited references provide suggestion or motivation to combine with any other reference or with knowledge available to one of ordinary skill in the art to provide the claimed invention. Such a suggestion to so combine the cited references is this believed to be the result of impermissible hindsight.

Accordingly, the cited references failing to provide all the elements of the claimed invention, failing to suggest or provide motivation to provide such elements or to be combined in an attempt to do so, and failing to provide a reasonable expectation of success for such a combination, Applicants respectfully submit that the rejections of Claims 1-3, 5-11, and 22-27 under 35 U.S.C. §103(a) are overcome.

CONCLUSION

Applicants believe all rejections to be overcome as discussed above, and respectfully request the entry of the amendments, reconsideration and allowance of all pending claims. All claims being believed to be in *prima facie* condition for allowance, an early action to that effect is respectfully solicited.

If any rejections or objections remain, Applicants request that an interview with the Examiner, either in person or via telephone, before the issuance of the next Action in this case to allow discussion of such issues as may remain.

Please charge any additional fees, including any fees for extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39766-0072 A2**.

Respectfully submitted,

Dated: August 9, 2004

By: _____
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STATEMENT

The undersigned attorney of record hereby states that the hybridomas HER4.10H1.1A1 (PTA-2828), HER4.1C6.A11 (PTA-2829), HER4.3B9.2C9 (PTA-2826), HER4.1A6.5B3 (PTA-2827) and HER4.8B1.2H2 (PTA-2825) have been deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, Va. 20110-2209, USA (ATCC) on December 19, 2000.

The deposit of the hybridomas with the ATCC was made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures the maintenance of a viable culture of the deposit for 30 years from the date of deposit or for 5 years after the last request for a sample or for the enforceable life of the patent whichever is longer. The deposit will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 U.S.C. §122 and the Commissioner's rules pursuant thereto (including 37 C.F.R. §1.14 with particular reference to 886 OG 638).

Date: August 9, 2004

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